EXPERIMENT

5

Cobaloximes: Models of Vitamin B_{12} A Demonstration of "Umpolung" in the Reactivity of an Organometallic Complex

REFERENCES

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SAFETY RECOMMENDATIONS

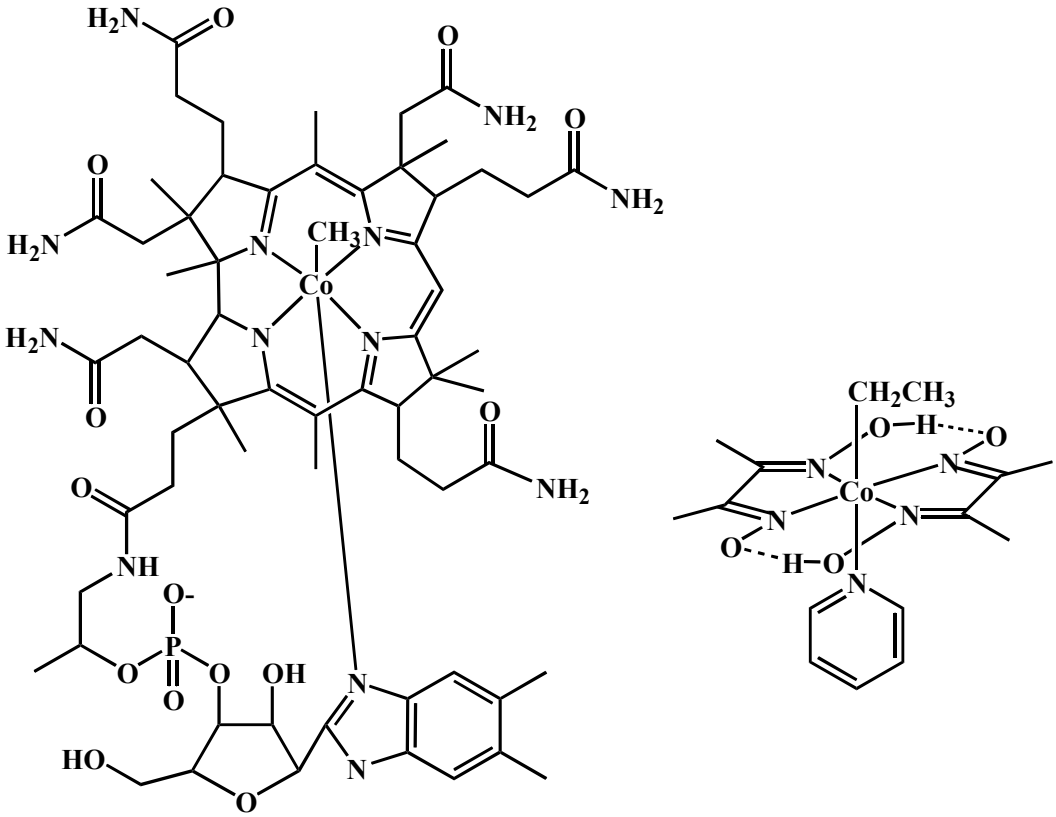
Pyridine: Pyridine is harmful if swallowed, inhaled or absorbed through the skin. It has a noxious smell and is a general anesthetic. Dispense it only in the hood. Wash all utensils in contact with pyridine in the hood with acetone.

Pyridine, bromine and bromoalkanes are toxic and should only be handled in the hood.

INTRODUCTION

Cobaloximes have been prepared[1,2] and studied extensively as model compounds for the coenzyme vitamin B12. These compounds exist at the interface of classical coordination chemistry, organometallic chemistry, and bioinorganic chemistry.

The metal site of vitamin B12 consists of a cobalt atom coordinated by a tetrapyrrole macrocyclic ligand called a corrin (see structures below). One of the axial sites is occupied by a 5,6-dimethylbenzimidazole nucleotide. The key feature of the vitamin.'s biochemical activity is its ability to form metal-alkyl (Co.–C) bonds in the second axial site. The N4 macrocycle in the cobaloxime model complexes is made up of two monodeprotonated dioxime molecules linked at two points by hydrogen bonding. The result is an essentially planar macrocyclic ligand. The most common cobaloximes utilize the dimethylglyoxime ligand. The structure shows a typical cobaloxime model complex. A very large number of model complexes have been prepared in which both the neutral ligand and the alkyl ligand are varied.[1,2]



Structural comparison of vitamin B_{12} derivative (left) and a cobaloxime model complex (right).

Alkyl or aryl derivatives of cobaloximes (CbCoX) are routinely prepared by two general routes. A carbanionic reagent (such as PhMgBr) reacting with a Co(III) halide results in a nucleophilic displacement of the halide ion. In the second method, Co(III) is

converted to Co(I) using a variety of reducing agents (such as $NaBH_4$). In acidic or neutral solution, a cobalt hydride species exists, while under sufficiently basic conditions, the Co(I) species has significant anionic character and behaves as an exceedingly powerful nucleophile. Reaction of the Co(I) species with a wide variety of electrophiles generates an organocobaloxime (RX). In the organocobaloxime compounds, the cobalt formally exists in a +3 oxidation state, with the carbon ligand being assigned a charge of –1.

$$CbCoBr + PhMgBr \longrightarrow CbCoPh + MgBr_2 \quad (1)$$

$$CbCoBr \xrightarrow{NaBH_4} CbCo^- \quad (2)$$

$$CbCo^- + CH_3I \longrightarrow CbCoCH_3 + I^- \quad (3)$$

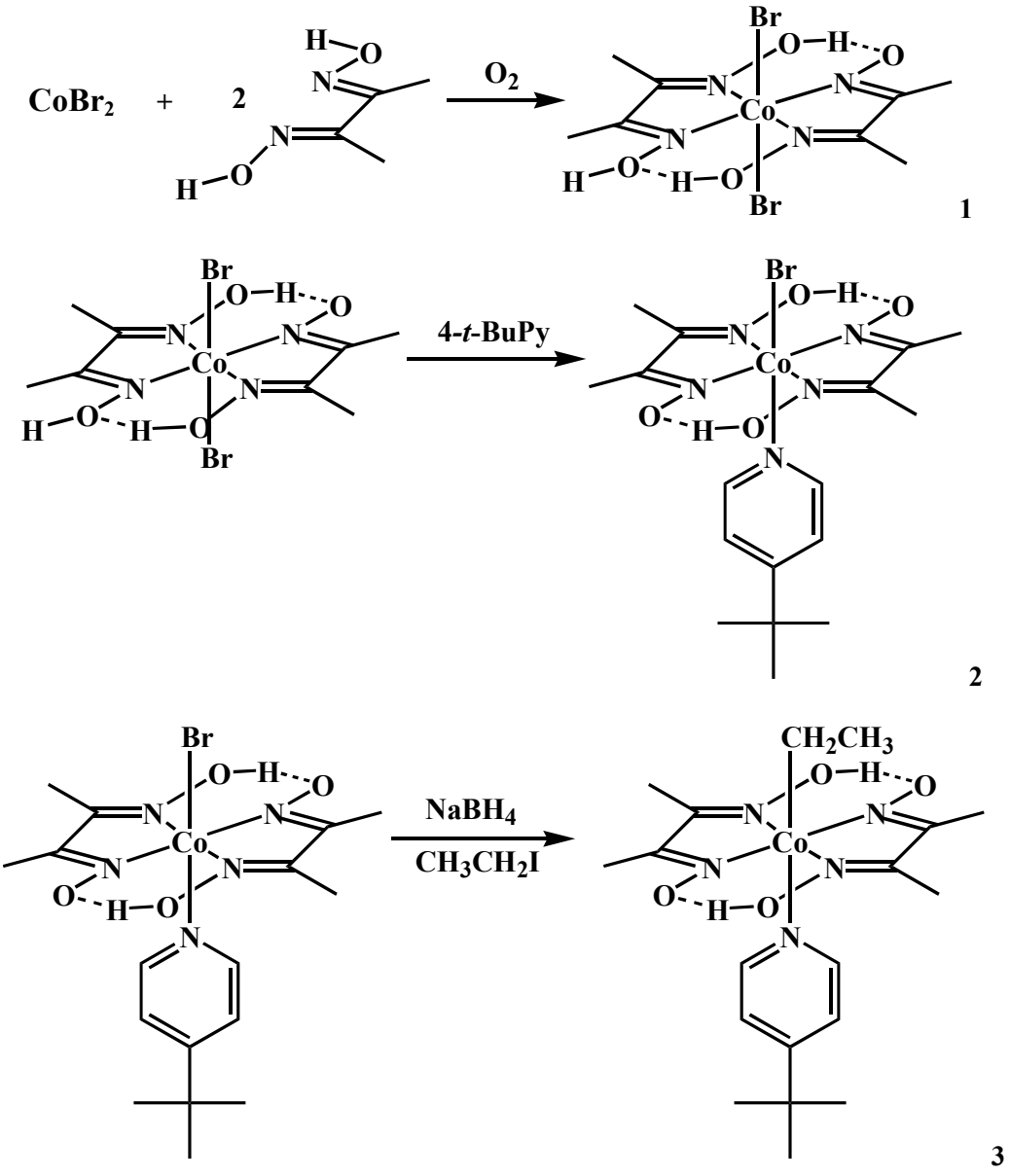
The reversal of reactivity displayed by this organometallic system has parallels in classical organic chemistry. Alkyl halides (carbon in a higher oxidation state) behave as electrophiles and readily undergo nucleophilic displacement of the halide atom (eq 4). This sense of reactivity can be reversed by reducing the alkyl halide (for instance by conversion to a Grignard reagent using elemental magnesium; eq 5). These reagents (where carbon is now in a lower oxidation state) are very nucleophilic and can react with a variety of electrophiles (eq 6). Seebach has coined theterm “umpolung” to describe this reversal of reactivity.[4]

$$RX + R'^- \longrightarrow R–R' \quad (4)$$

$$RX + M^0 \longrightarrow RMX \quad (5)$$

$$RMX + R'–X' \longrightarrow R–R' + MXX' \quad (6)$$

Syntheses of cobaloxime derivatives have been reported in two volumes of Inorganic Synthesis[4,5] and there are at least five published laboratory experiments based on the preparation of cobaloximes[6 -10]. The original Inorganic Synthesis preparation of cobaloxime derivatives[4] suffers drawbacks that preclude its conversion to a useful laboratory exercise. Several of the derivatives are of such low solubility that characterization by NMR is difficult. Subsequent work by Marzilli has shown[11] that the procedure for preparation of



Scheme I: Synthesis of cobaloxime derivatives

$Co(dmgH)_2(Py)Cl$ leads to large amounts of a salt, $[Co(dmgH)_2(Py)_2][Co(dmgH)_2Cl_2]$, in addition to the desired complex. In that same paper, Mazilli describes a more reliable, two-step procedure for preparing $Co(dmgH)_2(RPy)Cl$. Both Marzilli[11] and Bulkowski et al.[5], in the second Inorganic Synthesis procedure, have used 4-tert-butylpyridine as the axial base, thus increasing the solubility and facilitating characterization by NMR. The final refinement of the original Inorganic Synthesis procedure is to prepare organocobaloximes via alkylation of a Co(I) intermediate prepared by reduction of the Co(III) precursor. Although Bulkowski et al.[5] state that this procedure gives more reproducible yields and higher quality product, it is still common practice to prepare organocobaloximes in situ from mixtures of cobalt(II) salt, dioxime ligand, sodium borohydride, and electrophile[12]. Three of the published experiments describe the in situ preparation of organocobaloximes without adding $NaBH_4$ [7-9]. In this case, the Co(II) intermediate disproportionates to the reactive Co(I) and Co(III). This method, while very rapid and technically straightforward, is seldom encountered in the research literature because it suffers the obvious disadvantage of a maximum 50% yield based on cobalt and ligand. The procedure described here incorporates all of the aforementioned improvements.

The following scheme will be used to form a methylcobaloxime model of vitamine B12 The Co(I) intermediate generated in the course of preparing the very stable $Co(dmgH)_2$(4-**t**-BuPy)Et is very air-sensitive and failure to maintain strictly anaerobic conditions will result in greatly diminished yields and very impure product. Compounds 1 and 2 (Scheme I) may be made in a single day, and compound 3 (Scheme I) may be prepared during the second lab period. These low-spin d6 compounds can be characterized by IR and NMR spectroscopy.

In your module report, make sure you address the following issues:

1. Balance all reactions (include all side products).
2. Explain the role of O_2 in this module.
3. Assign oxidation states of all your products.
4. Characterize your products and assign your spectral peaks.

PROCEDURE

1st Lab Period

Synthesis of Dibromo(dimethylglyoxime)(dimethylglyoximato)cobalt(III) (1)

Add 1.10 g dimethylglyoxime (9.5 mmole) to a stirred solution of 1.50 g of cobalt(II) bromide hydrate (4.59 mmole) in 25 mL of acetone. As a very gentle stream of air is played over the solution a green solid will be deposited. After 1h, chill the solution on ice, filter, and wash with 2 x 10 mL of cold acetone. The yield of green microcrystalline product is 1.8-2.0 g (85-95% yield based on CoBr2). The compound can be characterized with IR.

Synthesis of Bromo(4-tert-butylpyridine)cobaloxime (2)

Suspend 1.8 g (3.89 mmole) of the green product (1) from the first step in 40 mL of methanol. Add 1.10 g (1.21 mL, 8.1 mmole) of 4-tert-butylpyridine. Stir the mixture until the green solid disappears and is replaced by a brown crystalline solid (20-30 min). Add water (60 mL) with stirring and cool the suspension in ice for 10 min. Collect the product by suction filtration and wash with 3 x 10 mL of 2:1 water/methanol and 2 x 10 mL of diethyl ether. The yield of the brown microcrystalline solid is about 1.8 g (89%).

2nd Lab Period

Synthesis of Ethyl(4-tert-butylpyridine)cobaloxime (3)

Dissolve 0.2 g KOH in 20 mL of methanol in a 100 mL round-bottom flask. Fit the flask with a Claisen-head that has a stopper on the straight arm and a septum, with a needle outlet, on the curved arm. Add 0.75 g (1.50 mmole) of bromo(4-tert-butyl-pyridine)cobaloxime (2) as a solid through the stopper end. Chill the homogenous mixture in an ice/salt bath (to about –10 oC) and thoroughly deaerated with N_2 (~10 min). Add sodium borohydride (0.15 g, 3.9 mmole) carefully

through the stopper end against a positive nitrogen flow. The mixture should turn rapidly to a dark blue-green color. Stir the solution for 5 min and add 0.50 mL (0.98 g, 6.3 mmole) of ethyl iodide using a syringe (against a positive nitrogen flow). The mixture will immediately turned red-brown. Stir in the ice bath for 20 to 30 min. Quench the reaction with acetone (3 mL) and water (30 mL). Reduce the volume to 50 mL with nitrogen, giving an orange crystalline solid. Chill the flask in an ice bath, filter the orange solid and wash with water. The yield for this step is 1.0-1.2 g (73-88%). The compound is sufficiently pure (by NMR), but it may be recrystallized by dissolving in methanol, adding an equal volume of water, and reducing to half volume by evaporation.

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